

Cellular Adaptations

Cellular Injury

The mechanisms of cell injury can be anything. Cells live in a tightly regulated balance that requires constant supply of oxygen and glucose to sustain oxidative phosphorylation, the Na^+/K^+ -ATPase, and the electrochemical gradient that surrounds the cell. In addition to energy, cells need cofactors (vitamins) for their cellular processes. Competing organisms (infection) can attempt to take over. The host immune system (inflammation, autoimmune) can fight against the cells. These are two advanced organizers that I have not found very useful in clinical practice, but they do seem to help people start studying. These tables show how cells can get injured and what they might have to adapt to. The rest of the lesson covers what cells can do in order to adapt.

PO ICING		VINDICATES	
<u>P</u> hysical agents	Heat, cold, trauma	<u>V</u> ascular	Poor perfusion, thrombosis
<u>O</u> xygen deprivation	Oxidative phosphorylation	<u>I</u> nflammatory	"-itis"
<u>I</u> nfections	Bacterial, viral, fungal	<u>N</u> eoplasia	"-oma"
<u>C</u> hemical	Poisons, drugs, toxoids	<u>D</u> egenerative	
<u>I</u> mmune	Autoimmune, anaphylaxis	<u>I</u> diopathic	
<u>N</u> utrition	Malnutrition	<u>C</u> ongenital	
<u>G</u> enetic		<u>A</u> cquired	
		<u>T</u> rauma	
		<u>E</u> nvironment	
		<u>P</u> sychiatric	

Table 1.1: Advanced Organizers for Mechanisms of Cellular Injury

This is a warmup lesson with a warmup table.

Cellular Adaptation

The spectrum of cell response to injury and other stimuli is immense, and responses are determined both by the type of cell and the type of stimulus. A cell can receive an insult so great that it **cannot adapt** and it is killed (**necrosis**). A cell can be told it should die, recognize it's not needed, or realize it is so badly damaged that it dies (**apoptosis**). Or it can adapt. **Added stress** can cause a change. The **absence of stress** can cause a change. We discuss necrosis in Lesson #2 and apoptosis in Lesson #3. Here, we review the different ways a cell can change.

Cellular Adaptation: Cell Size = Hypertrophy and Atrophy

Cells can undergo **hypertrophy**, whereby the cells **increase in size** while the **number of cells remains the same**. Cells that are differentiated and arrested in the G₀ phase of the cell cycle are called **permanent cells**. Because they cannot re-enter the cell cycle, their response can be only in the change of size, not number. For example, skeletal muscle hypertrophies in bodybuilders, cardiac muscle enlarges when it fights against hypertension, and even smooth-muscle renal arterioles get thickened when stressed by hypertension. Other cells can change size, but permanent cells can **only change size**.

The opposite of hypertrophy is **atrophy**, whereby the cells **decrease in size** while the **number of cells remains the same**. In addition, there is often a **reduction in organelle quantity**. Inactive cells “use it or lose it.” Just as there is an increase in size of permanent cells when stressed, so too is there a decrease in size of permanent cells when destressed. That bodybuilder who stops lifting weights will lose the muscle. But he “loses muscle” in the sense that the thing he looks at in the mirror when he flexes is smaller in size because the skeletal muscle cells are smaller in size, but no change in the number of cells ever occurs. The neurons of the brain atrophy in dementia. Both the cells and the organ shrink in size. Other tissues that are not permanent can undergo atrophy and hypertrophy, but permanent cells can **only** adapt with atrophy and hypertrophy. The thinning of the renal cortex in hydronephrosis or the decreased size of glands when provided exogenous hormones are examples of nonpermanent cells atrophying.

Be careful about context. The word atrophy can also refer to the **organ's getting smaller**, but the mechanism could be either cells getting smaller or the number of cells decreasing. Cellular atrophy means the **cells are getting smaller**. This can happen with denervation, disuse, loss of blood supply, or poor nutrition.

Cellular Adaptation: Number of Cells = Hyperplasia and Hypoplasia

Cells can undergo **hyperplasia**, whereby the number of cells increases. The size of each cell stays the same, but the number of cells increases through cell division. These cells will either be **labile cells** (in the cell cycle already) or **stable cells** (in G₀, but can return to the cell cycle), or will be undergoing cell division anyway. For example, during the menstrual cycle (except menses), the endometrium of the uterus proliferates, or in a male prostate, hyperplasia causes enlargement of the prostate (the organ gets bigger because there are more cells). Hyperplasia is not considered premalignant, as evidenced by BPH's not being prostate cancer. Classic examples on testing include **psoriasis plaques** (hyperplasia of squamous epithelium), **phenytoin-induced gingival hyperplasia**, and the **goblet cells** induced by **chronic smoking**. Hyperplastic tissue implies an ongoing cell cycle, with increased number of cell divisions and opportunities for genetic errors, thereby increasing the risk of transformation to cancer. This is why endometrial cancer and prostate cancer exist—those tissues that are in the cell cycle can become malignant. While **hyperplasia itself is not premalignant**, a tissue that can undergo hyperplasia can have a malignant transformation.

Cellular Adaptation: Changing the Cell

Cells can undergo **metaplasia**, whereby the cells' number and size remain the same, but there is a **change from one cell type to another**. All of the genetic code exists in every cell. Cells are designed to differentiate into a certain cell type. But when exposed to severe stress, it's possible that another region of DNA is accessed, and an already differentiated cell changes to another differentiated type of cell. This is an **adaptive response**, from the cell's perspective. But “*changing the way a cell uses DNA*” sounds an awful lot like “*cancer*.” Examples include the **lower third of the esophagus exposed to acid reflux** (esophageal squamous epithelium cannot tolerate acid content, so they change to duodenal goblet cells that can) or **bronchial epithelium in smokers** (cilia change to squamous epithelium). Finally,

HPV infection induces a **columnar epithelium** to change to **squamous** in cervical tissue. **Metaplasia** **itself is not premalignant**. But the metaplastic change increases the risk of malignant transformation substantially (there is a 40x higher chance of esophageal cancer with Barrett's esophagus, the eponym for metaplastic transformation of the esophagus, when compared to the general population).

Dysplasia is premalignant. It's a **disordered proliferation** of cells with the **loss of size, shape, and orientation**. Epithelial layers should be consistent cells that look the same, do the same thing, and align themselves in sheets. Dysplasia is when the cells look different from each other, change shape, or aren't perfect copies of each other. The intensity of dysplasia is based on the layer depth involved within an epithelium. The more cells there are in an epithelial layer that demonstrate the dysplastic change, the more severe the grading. Mild dysplasia has few layers, moderate dysplasia has some but not all, and then severe dysplasia, also called carcinoma in situ, has the entire epithelial layer as dysplastic tissue, but without invasion of the basement membrane.

Neoplasia is the uncontrolled **clonal proliferation** of cells. Neoplasms can be benign (no invasion) or malignant (invasion). Be careful with the terminology. Idiomatically, cancer, neoplasia, and malignancy are used interchangeably. The strict definition of neoplasia is only the unregulated growth of cells.

Anaplasia. Complete lack of differentiation. The degree of anaplasia reveals how primordial a cell has become. Anaplasia is always malignant. The cell loses expression of differentiated proteins and reverts to the primordial gene expression. An anaplastic cancer is always bad.

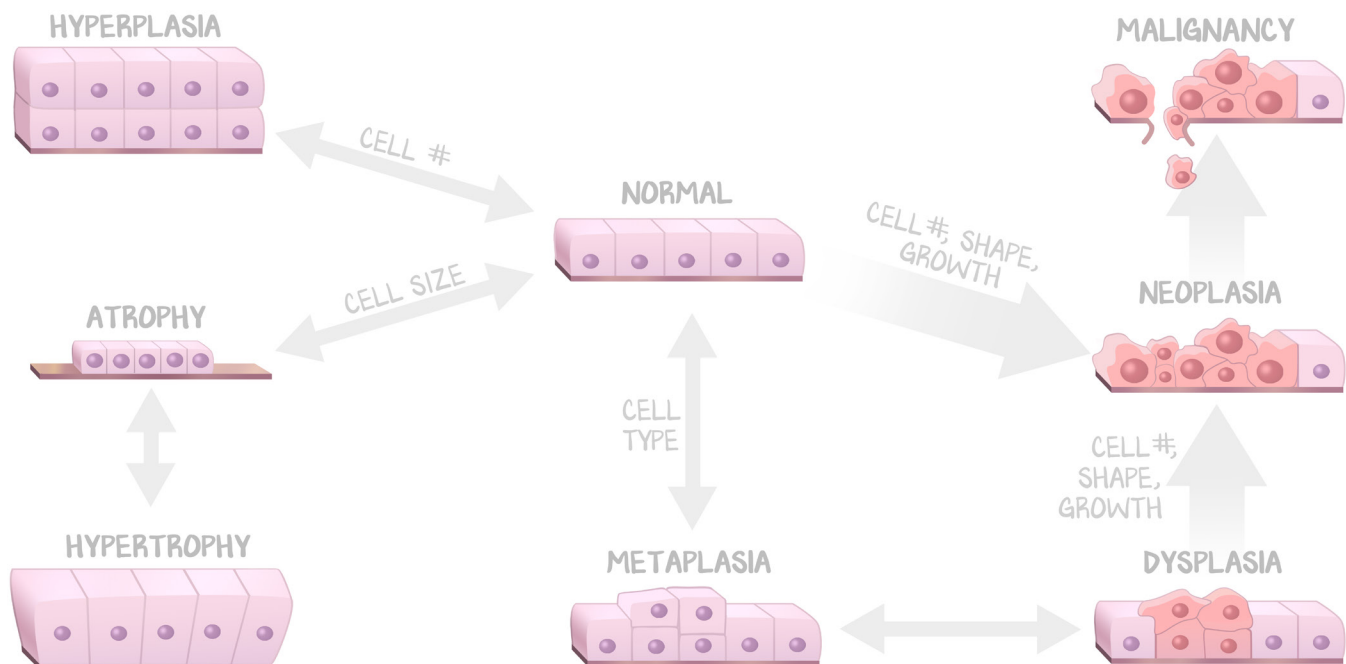


Figure 1.1: Cellular Response to Stress

All the responses to stress, not taking into account the cell type. Cells can get bigger (hypertrophy) or smaller (atrophy), increase in number (hyperplasia), change type (metaplasia), or become cancerous (dysplasia). If unregulated cell division continues (neoplasia), the cells can progress to invasion (malignant).

Cellular Disease Processes

Sometimes the cells exposed to a stress die. Other times they become malignant. In Lessons #2 *Necrosis* and #3 *Apoptosis*, we will explore how cells die. Necrosis (killed by a stressor) is very different than apoptosis (careful, purposeful deconstruction of a cell). Both are considered “cell death,” but we will break that mold to help you keep the differences straight.

In Lesson #4 *Wound Healing*, we will discuss how the processes of **hyperplasia** and **metaplasia** can be useful. This looks at organ-level repair and leverages the concepts learned up to that point to bridge the gap between “normal healing processes” and “what cancer does to sustain itself.”

Malignant Transformation

We get into the details of the **cell cycle**, **mitosis**, and **cell cycle regulation** in Lessons #5 and #6. We lay down the physiology of what should happen, then use it to understand how it breaks in #7 *Biology of Cancer*, and how we treat it in #8 *Cycle Chemotherapy*. We close the series with the clinical impact of malignancy beyond the physiology and pathology in #9 *Epidemiology of Cancer*, #10 *General Concepts of Neoplasia*, and #11 *Diagnosing Cancer*.